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Evaluation of Risk Factors for Infectious Morbidity in Postoperative Gynecologic Oncology Patients: A Time for a New Paradigm?

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Abstract

This study aimed to determine the postoperative fever index in the gynecologic oncology patient associated with significant infectious morbidity. A retrospective analysis was performed of 355 patients who underwent abdominal surgery. Charts were reviewed to evaluate postoperative temperature and risk factors for infectious morbidity. Statistical analyses were performed as indicated by the data type, including the Student *t* test, Mann-Whitney *U* test, χ^2 test, and 1-way analysis of variance. A value of $P < .05$ was considered significant. There were 210 patients with temperatures $< 100.5°F$ (group 1), 69 with a temperature $\geq 100.5°F$ to $< 101°F$ (group 2), and 76 with a temperature $\geq 101°F$ (group 3). Demographic data were similar among groups. There were 285 diagnostic tests performed, with 51 test results indicative of infectious morbidity. Patients in group 3 underwent more testing and had more positive test results compared with groups 1 and 2. The majority of diagnostic testing and positive test results (60%) were in patients from group 3. Groups 1 and 2 were statistically similar in the number of positive test results and antibiotic duration, demonstrating a lower risk of infectious morbidity compared with group 3. This study suggests that a postoperative temperature of $\geq 101°F$ appears to be a better predictor of significant infectious morbidity compared with the prior definition of a temperature $\geq 100.5°F$. Furthermore, this illustrates the need for the development of a postoperative temperature evaluation protocol to avoid expensive evaluations and empiric treatment of benign causes of postoperative fever.

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Introduction

Clinicians are frequently faced with early postoperative fever in surgical patients. This is especially true of gynecologic oncology patients after abdominal surgery. Incidence of febrile morbidity in gynecologic patients ranges from 5% to 75%, depending on the definition of fever.[1] Regardless of the high incidence of fever, infectious etiology is rarely the cause in this patient population.[2] Over 90% of febrile morbidity is linked to noninfectious etiology. Numerous studies support these findings and cite alternative causes for early postoperative fever, including cytokines, interleukins, and other causes of inflammation.[2-5] Not only are these fevers often not due to infectious causes, but also they often resolve spontaneously without any intervention.[6] Despite this, fevers encountered in the early postoperative period are often evaluated with costly and nonuniform approaches. It is not uncommon for such patients to undergo multiple blood and urine cultures, urinalyses, chest radiographs, computed tomography (CT) scans, and serum testing. In addition to extensive evaluations, empiric antibiotics are frequently started in conjunction with the evaluation, without a clear diagnosis being identified.

The definition of postoperative fever has been a source of controversy and ambiguity, often leading to more confusion than clarity for physicians. Historically, the most frequent definition, as described in *Te Linde's Operative Gynecology*,[7] is a "temperature of

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38°C (100.4°F) or greater on 2 occasions, at least 6 hours apart, more than 24 hours after the surgical procedure." This definition has been supported in many publications on postoperative fever.[8-14] Studies have recently indicated that this definition may be in error and lead to unnecessary testing and concern. Lyon et al[8] reviewed 257 postoperative gynecologic patients, publishing data supporting that the commonly used threshold of 38°C was not as discriminatory as 38.3°C (100.9°F) in detecting postoperative morbidity. Frequency of temperature greater than 38.4°C (101.1°F), as well as the absolute degree of elevation, was suggested to relate to the morbidity level. The definition of significant fever used by Lyon et al[8] was at least 2 spikes of the temperature $\geq$ 38.4°C in the postoperative course. The suggested definition of postoperative fever as $\geq$ 101°F may improve discrimination between ill patients and those with transient and inconsequential temperature elevations; however, in the clinical setting, the seemingly more prevalent concept of significant postoperative fever includes a "diagnosis by the attending physician, without apparent criteria," as cited by Shapiro et al[15] in 1982 and revisited by Lyon et al[8] in 2000.

This review sought to retrospectively evaluate and identify the fever index and risk factors associated with infectious morbidity in the postoperative abdominal surgical patient in the gynecologic oncology population to better identify significant postoperative fever and potentially decrease the incidence of expensive evaluations and empiric treatment of benign causes of postoperative fever.

Patients and Methods

A retrospective chart review of 355 patients from the gynecologic oncology service undergoing open abdominal surgery between 1999 and 2007 at the Medical University of South Carolina was performed using the departmental billing database. Approval from the institutional review board was obtained. Patients were cross-referenced through an internal departmental database of all gynecologic cases. Additional patients identified in the database were added to the pool. Patients with postoperative fever defined as temperature $\geq$ 100.5°F on at least 1 occasion were identified by extensive review of the nursing records and vital sign documentation. Patients without this documented fever were considered as the control population.

Baseline demographic data and medical history were collected. Potential risk factors for infectious morbidity including preoperative antibiotic use, blood loss, extent of tumor spread, intraoperative antibiotic use, and incidence of intraoperative and postoperative blood transfusion and duration of bladder catheterization were noted. Wound contamination was defined as the contamination of the abdomen with bowel contents as noted in the operative report. Onset of fever (hours postoperatively) and maximum fever temperature were recorded. Fever evaluations including urine and blood cultures, chest radiographs, and CT scans were collected. Positive chest radiograph findings were defined as a diagnosis of pneumonia, whereas atelectasis and "low lung volumes" were considered negative. Similarly, positive CT scan findings were defined as a diagnosis of pneumonia or abscess, whereas pulmonary embolus and atelectasis diagnoses were defined as negative. Antibiotic use and duration were recorded. Prophylactic antibiotic use was defined as preoperative antibiotic use given before skin incision. Intraoperative antibiotic use was defined as the use of antibiotics during surgery, accounting for the standard of care in the addition of antibiotics for concomitant bowel surgery or for re-dosing based on blood loss and length of surgery.

The data were separated into groups based on maximum postoperative temperature, including temperature $<$ 100.5°F (defined as the control group, group 1), temperature $\geq$ 100.5°F to $<$ 101°F (group 2), and temperature $\geq$ 101°F (group 3). Inclusion into groups 2 and 3 required only 1 temperature in the aforementioned range, occurring at any time in the postoperative period. Continuous predictors were evaluated using the Student *t* test and Mann-Whitney *U* test as appropriate. Categorical predictors were compared using the χ^2 test or Somers D test for ordinal data. A value of $P < .05$ was considered significant.

Results

A total of 355 gynecologic oncology patients met inclusion criteria; of those, 210 (59%) did not have a recorded temperature greater than 100.5°F and were considered the control in this analysis. There were 145 patients (41%) who met the criteria for febrile morbidity; 69 (48%) had a temperature between 100.5°F and $<$ 101°F, and 76 (52%) had a fever $\geq$ 101°F. Demographic data and medical comorbidities are shown in Table 1. The median ages among groups 1 through 3 were 56.7, 56.2, and 50.3 years, respectively (range, 16-89 years). The women in group 3 were significantly younger ($P = .006$). The majority of women in all groups were white, although groups 1 and 2 had a significantly higher percentage than group 3 (67.2% vs. 72.5% vs. 52.6%, respectively; $P = .03$). There were no significant differences in weight, body mass index, parity, or medical comorbidities among the 3 groups.

Clinicopathologic characteristics including preoperative, intraoperative, and postoperative factors were examined (Table 2). There were no significant differences in preoperative characteristics among the groups, including preoperative laboratory values; preoperative hemoglobin, hematocrit, and white blood cell count; preoperative length of hospital stay; or blood transfusion rates before surgery. Prophylactic antibiotics were used in over 97% of all patients, with no difference between the 3 temperature groups. Intraoperative factors were similar among groups, with no differences in operative time, estimated blood loss, wound contamination, intraoperative antibiotic use, incidence of disseminated cancer, choice of surgical incision, or intraoperative blood transfusion rate. There were no differences in the rates of postoperative wound infection, duration of urethral catheterization, use of nonsteroidal anti-inflammatory drugs, or postoperative laboratory findings (hemoglobin, hematocrit) among the groups. The median maximum temperature was significantly different between groups 2 and 3 ($P < .0001$), with medians of 100.7°F (range, 100.5°F-100.9°F) and 101.6°F (range, 101°F-103.7°F), respectively. The median onset of fever for both groups was after the first 24 hours, with groups 2 and 3 developing fevers at 33.5 and 31.8 hours postoperatively, respectively. The rates of blood transfusion were significantly higher in groups 2 and 3 (40.6% and 42.1%) compared with the control group (23.8%; $P = .002$). Postoperative antibiotic use was significantly higher in group 3 compared with groups 1 and

Table 1 Demographic Data and Medical Comorbidities by Temperature Group

Variable	Group 1: Afebrile (n = 210)	Group 2: ≥100.5°F to <101°F (n = 69)	Group 3: ≥101°F (n = 76)	P
	Median (Range) Mean (SEM)	Median (Range) Mean (SEM)	Median (Range) Mean (SEM)	
Age (years)	56 (16-89)	59 (16-83)	48 (23-84)	**.006**
	56.76 (±1.007)	56.2 (±1.86)	50.37 (±1.75)	
BMI	28.32 (18.2-54.3)	27.52 (17.5-50.2)	29.74 (17.5-68.3)	.58
	29.72 (±0.56)	29.55 (±0.88)	30.81 (±1.12)	
Parity	2 (0-6)	3 (0-5)	3 (0-3)	.29
	1.995 (±0.079)	2.175 (±0.15)	2.206 (±0.14)	
	n (%)	**n (%)**	**n (%)**	
Race				
White	141 (67.2)	50 (72.5)	40 (52.6)	**.03**
Black/Other	69 (32.8)	19 (27.5)	36 (47.3)	
CHF History	5 (2.3)	0 (0)	0 (0)	.09
Stroke History	4 (1.9)	1 (1.4)	1 (1.3)	.93
Hypertension	88 (42)	23 (33.3)	30 (39.5)	.43
Diabetes	31 (14.8)	7 (10.1)	16 (21.1)	.18
Insulin Use	9 (4.3)	1 (1.4)	4 (5.3)	.47
COPD	2 (1.0)	1 (1.4)	2 (2.6)	.87

Bolded data represent statistically significant values.
Abbreviations: BMI = body mass index; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; SEM = standard error of the mean.

2 (70% vs. 16.7% vs. 50.7%, respectively; $P < .001$). Analysis of postoperative antibiotic use among individual groups found significant differences as well (group 1 vs. group 2, $P = .0001$; group 1 vs. group 3, $P = .0001$; group 2 vs. group 3, $P = .03$). Similarly, the duration of postoperative antibiotic use ($P = .001$), as well as the length of postoperative hospital stay ($P = .0003$), were significantly longer in group 3 compared with groups 1 and 2.

The number of evaluations for infectious etiologies in the postoperative period was recorded. The numbers of urine cultures, chest radiographs, CT scans, and blood cultures obtained were significantly higher in group 3 compared with groups 1 and 2 ($P < .0001$) (Table 3). Of the 119 urine cultures obtained, only 20 (16.8%) had positive results. More urine cultures were obtained with rising temperatures ($P < .0001$); however, the percentage of cultures with positive results per group was highest in group 1 (27.3%), followed by group 2 (20.6%), and was the lowest in group 3 (11.1%). This was not significant ($P = .07$) (Table 4).

Data were also collected on imaging evaluations including chest radiographs and CT scans. Chest radiographs were ordered for 114 patients (32.1%) among all groups, but only 19 (16%) had positive findings indicating an infectious cause. A significantly higher number of chest radiographs was obtained in groups 2 and 3 compared with group 1 ($P < .0001$) (see Table 3). Despite the increasing number of radiographs ordered in groups 2 and 3, similar rates of positive chest radiograph findings were present among the respective temperature groups (15%, 15.6%, and 17.8%, respectively; $P = .9$) (see Table 4). CT scans were obtained on 12 patients (9 with positive findings), all in group 3 with a fever ≥ 101°F.

Blood cultures were collected for a total of 40 patients, with the majority collected in group 3 (85%). The collection of blood cultures was standardized to 2 blood cultures obtained from 2 separate sites for all patients. There were 3 blood cultures with positive results, all in group 3 with a fever ≥ 101°F. This represents 7.5% of all blood cultures obtained.

Clearly, the number of tests obtained was significantly higher in group 3 compared with groups 1 and 2 (165 vs. 52 vs. 68, respectively; $P < .0001$) (Table 5). Whereas 39 patients in the control group had a total of 52 tests obtained, 44 patients in group 2 underwent 68 tests, and 68 patients in group 3 had 165 tests performed. The number of patients with positive test results per group was significantly higher in group 3 compared with groups 1 and 2 ($P < .0001$) (see Table 5). Patients with positive test results among groups 1, 2, and 3 represented 4.2%, 16%, and 28.9%, respectively. When comparing those patients with at least 1 positive test result, there was no difference between groups 1 and 2 ($P = .8$). However, the number of patients with at least 1 positive test result in group 3 was significantly higher compared individually with group 1 ($P = .0002$) and with group 2 ($P < .001$). Overall, 19.6% of positive test results were in the control group and 23.5% were from group 2, whereas group 3, with a temperature > 101°F, accounted for 56.9% of the positive test results ($P < .0001$) (see Table 5).

Discussion

Postoperative fever is a common finding in the gynecologic oncology patient after extensive open abdominal surgery. Although the formal definition of postoperative fever requires 2 separate documented temperature values, in many instances, it has become reflex nature among providers to order costly, intensive, and invasive tests to evaluate for possible etiologies of fever based on 1 temperature value. The present data analysis required 1 temperature value

Table 2 Clinicopathologic Characteristics by Temperature Group

Operative Factor	Group 1: Afebrile (n = 210) Median (Range) Mean (SEM)	Group 2: ≥100.5°F to <101°F (n = 69) Median (Range) Mean (SEM)	Group 3: ≥101°F (n = 76) Median (Range) Mean (SEM)	*P*
Fever Maximum Temperature (°F)	N/A	100.7 (100.5-100.9) 100.7 (±0.01737)	101.6 (101-103.7) 101.7 (±0.06914)	**<.0001**
Preoperative WBC Count (cells/μL)	7.18 (2.1-30) 7.63 (±0.2063)	6.94 (2.5-11.4) 7.04 (±0.2493)	7.09 (3.5-23) 7.57 (±0.3612)	.33
Surgery Duration (min)	201 (45-580) 214.3	197 (74-591) 218.6	184.5 (50-428) 207.5	.76
Duration of Urethral Catheterization (h)	43.29 (5.6-347) 50.89	45.25 (5-94.5) 45.14	48.13 (17-314) 60.32	.10
Estimated Blood Loss (mL)	475 (0-4000) 630.1	425 (50-4600) 666.3	450 (50-4500) 635.0	.92
Onset of Fever (Hours Postoperatively)	N/A	33.5 (0-125.3) 36.72 (±2.701)	31.88 (0-230.8) 37.71 (±4.381)	.85
Duration of Postoperative Antibiotic Use (h)	52 (10-336) 92.38 (±14.62)	72 (6-288) 91.33 (±13.50)	120 (10-504) 164.9 (±17.65)	**.0011**
Length of Hospital Stay (d)	4.92 (1.8-24.4) 5.71 (±0.22)	6.03 (2.2-29.7) 6.8 (±0.49)	6.21 (2.9-22.9) 7.68 (±0.51)	**.0003**
	n (%)	**n (%)**	**n (%)**	
Radical Hysterectomy	50 (23.8)	17 (24.6)	22 (28.9)	.67
Wound Contamination, Intraoperative	1 (.5)	2 (2.9)	1 (1.3)	.6
Wound Infection, Postoperative	3 (1.4)	2 (2.9)	5 (6.6)	.07
Prophylactic Antibiotic Use	205 (97.6)	68 (98.6)	73 (96.1)	.52
Intraoperative Antibiotic Use	60 (28.6)	16 (23.2)	23 (30.3)	.57
Postoperative Antibiotic Use	35 (16.7)	35 (50.7)	53 (70)	**<.0001**
Disseminated Cancer	53 (25.2)	22 (31.8)	22 (28.9)	.56
Vertical Skin Incision	188 (89.5)	60 (87)	62 (81.6)	.07
Postoperative pRBC Transfusion	50 (23.8)	28 (40.6)	32 (42.1)	**.002**
NSAID Use	94 (44.8)	30 (43.5)	29 (38.2)	.51

Bolded data represent statistically significant values.
Abbreviations: N/A = not applicable; NSAID = nonsteroidal anti-inflammatory drug; pRBC = packed red blood cells; WBC = white blood cells.

for inclusion into groups 2 and 3 to evaluate the risk of febrile morbidity within a given temperature range. Additionally, it has long been recognized that a large contributor to postoperative fever is the inflammatory and immune response of the body to tissue damage and destruction.[2,5,6] Release of cytokines, interleukins, tumor necrosis factors, and other endogenous pyrogens is a significant contributor to postoperative fever that can lead to expensive and unnecessary evaluations searching for an infectious etiology that will never be found.

Risk stratification has been identified as a possible strategy for reducing excessive evaluations and cost in the setting of early postoperative fever. Stratifying patients into low-risk and high-risk categories and standardizing evaluation and treatment based on that stratification has been found to decrease the use of empiric antibiotics without compromising morbidity in low-risk gynecology patients.[2] Identifying risk factors associated with significant postoperative morbidity is essential to improve the care of gynecologic oncology patients by avoiding unnecessary testing and treatment of those without true pathology while promptly and adequately evaluating those patients with genuine etiology for fever. Traditionally, a temperature of 38°C (100.4°F) or higher after the first postoperative 24 hours usually prompts a "fever" workup, including history,

Table 3 Evaluation for Infectious Etiology by Temperature

Evaluation	Group 1: Afebrile (n = 210); n (%)	Group 2: ≥100.5°F to <101°F (n = 69); n (%)	Group 3: ≥101°F (n = 76); n (%)	*P*
Urine Culture	22 (10.5)	34 (49.3)	63 (82.9)	**<.0001**
Chest Radiograph	26 (12.4)	32 (46.4)	56 (73.7)	**<.0001**
Computed Tomography Scan	0 (0)	0 (0)	12 (15.8)	**<.0001**
Blood Culture	4 (1.9)	2 (2.9)	34 (44.7)	**<.0001**
Total Tests	52	68	165	Total: 285

Bolded data represent statistically significant values.

Table 4 Results Indicative of Infectious Etiology of the Evaluations Performed by Temperature Group

Evaluation	Group 1: Afebrile (n = 210); n (%)	Group 2: ≥100.5°F to <101°F (n = 69); n (%)	Group 3: ≥101°F (n = 76); n (%)	*P*
Positive Urine Culture Results	6 (27.3)	7 (20.6)	7 (11.1)	.068
Positive Chest Radiograph Findings	4 (15.4)	5 (15.6)	10 (17.9)	.95
Positive Computed Tomography Scan Findings	N/A	N/A	9 (75)	N/A
Positive Blood Culture Results	0 (0)	0 (0)	3 (8.8)	.45

Abbreviation: N/A = not applicable.

physical examination, and laboratory investigation. Unfortunately, many times a history and physical examination may be ignored in the reflexive ordering of diagnostic testing and laboratory evaluations.

The present evaluation confirms data in the literature in regard to management of postoperative "fever." Reflexive laboratory evaluation without regard to clinical evaluation appears to be alive and well. In a study of 676 patients with gynecologic disease (benign and malignant), 29% had a temperature of 100.4°F or greater, and 72% of those had no infection diagnosed. There were 760 tests performed, with only 17% yielding a positive result.[1] In the present study, 145 of 355 patients (41%) were noted to have a temperature elevation over 100.4°F, with only 76 (21%) having a temperature ≥ 101°F; 285 tests were ordered to evaluate possible infectious etiologies (consisting of urine cultures, blood cultures, chest radiographs, and CT scans), and only 51 (17.8%) were found to be indicative of an infectious cause. Recognition of risk factors that place a postoperative patient at risk for significant infectious morbidity is imperative for the appropriate testing and prompt treatment to quickly ensue. Similarly, recognizing when testing is not necessary for postoperative fever is just as important to avoid costly and invasive evaluations for noninfectious causes of fever.

In a comparison of the rate of positive test results among groups, there was no difference between groups 1 and 2. However, there were considerably more positive test results in group 3 compared with either group 1 ($P = .0002$) or group 2 ($P < .0011$). Those in group 3 with a temperature of ≥ 101°F represent a different group of postoperative infectious risk with a significantly higher percentage of positive test results compared with groups 1 and 2 ($P < .0001$) (see Table 5). Despite a few differences in the evaluation and management practices of groups 1 and 2, these 2 groups resemble each other more so in regard to risk of febrile morbidity compared with group 3. The significance of a temperature over 101°F in this patient population indicates that the control group and group 2 were statistically similar across almost all factors, whereas group 3 represented a separate risk category.

This study suggests that a postoperative temperature of ≥ 101°F appears to be the point at which there is a difference in the rate of positive test results and febrile morbidity, indicating the need for postoperative infectious evaluation in this population. With a very low return of positive laboratory test results in patients with temperature < 101°F, there appears to be very little or no indication to obtain tests reflexively in this population unless indicated on history and physical examination. The rates of positive chest radiograph findings in groups 1 and 2 are the same (15.4% and 15.6%), and they are similar to that of group 3 (17.9%), suggesting that in patients with temperature ≤ 101°F, chest radiographs are not a sensitive way to detect febrile morbidity. Given that there is no difference among all groups in regard to positive urine culture results and chest radiograph findings, additional information is required to evaluate the differences in regard to symptomatic evaluation using urine cultures and chest radiographs in the postoperative population compared with asymptomatic women. This may be an area of future study.

This study highlights several deficits in the management of postoperative fever. There were no protocols or guidelines for identifying what postoperative temperature is significant or what management should be prompted by it. The fact that several patients without a postoperative fever underwent laboratory testing for unknown reasons and that some patients were administered antibiotics other than prophylactic antibiotics at the time of surgery, also for unknown reasons, illustrates this problem. Whereas the majority of postoperative antibiotics were used in groups 2 and 3, there was no difference in the average duration of use of postoperative antibiotics in groups 1 and 2. Groups 1 and 2 were statistically similar in the number of positive test results and antibiotic duration, demonstrating a lower risk of infectious

Table 5 Evaluations Performed and Results by Temperature Group

Variable	Group 1: Afebrile (n = 210); n (%)	Group 2: ≥100.5°F to <101°F (n = 69); n (%)	Group 3: ≥101°F (n = 76); n (%)	*P*
No. of Patients Tested	39 (18.6)	44 (63.8)	68 (89.5)	**<.0001**
Percentage of All Tests With Positive Results Per Group (n = 51)	10 (19.6)	12 (23.5)	29 (56.9)	**<.0001**
No. of Patients With Positive Test Results (Per Group)	9 (4.2)	11 (16)	22 (28.9)	**<.0001**
No. of Tests Obtained Per Group (of 285 Tests Ordered)	52 (18.2)	68 (23.9)	165 (57.9)	**<.0001**
No. of Tests With Positive Results Per Group	10 (19.2)	12 (17.6)	29 (17.6)	.98

Bolded data represent statistically significant values.

morbidity compared with group 3. It does appear that women with postoperative fever of $\geq 101°F$ were more actively evaluated for an underlying infection, and although abnormal test results were uncommon, the highest number of positive test results was in this group. Therefore, it appears that a postoperative fever of $\geq 101°F$ is a better indicator of possible infection that needs further evaluation.

Conclusion

These findings warrant the consideration of a new paradigm in postoperative temperature evaluation, as well as the development of a protocol for the management of postoperative temperature. This protocol also should include a standard use of postoperative antibiotics. The reason for the use of postoperative antibiotics in afebrile patients is unknown and likely is provider preference. The implementation of a protocol regarding evaluation of postoperative temperature and the use of postoperative antibiotics is required to reduce the use of antibiotics, to reduce the use of diagnostic infectious testing, and to decrease medical costs. Patients with temperature $< 101°F$ should not undergo routine or reflexively ordered testing unless signs or symptoms of an infectious etiology are present on history and physical examination. The present data add to the pool of knowledge of evidence-based medicine in the postoperative open-abdominal surgical patient. This retrospective study, as well as others in the literature, suggests that a postoperative temperature of $\geq 101°F$ appears to be a better predictor of significant infectious morbidity compared with the prior definition of a temperature $\geq 100.5°F$. Furthermore, this study illustrates the need for the implementation of a postoperative temperature evaluation protocol to avoid expensive evaluations and empiric treatment of patients at low risk for infectious morbidity.

Disclosure

The authors have stated that they have no conflicts of interest.

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